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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/579,088	01/14/2008	Manzer Durrani		6451

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EXAMINER	
KAUFMAN, CLAIRE M	
ART UNIT	PAPER NUMBER
1646	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,088	DURRANI ET AL.	
	Examiner	Art Unit	
	CLAIRE KAUFMAN	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/14/08,4/21/08,8/24/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 5, 7, 19, 28-32 and dependent claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 5, 7, 19, 28 and 30 are unclear because of the use of the terms "native" and "variant'. While the specification says that ""native AAT" (alpha 1-antitrypsin) refers to AAT forms that can be isolated from natural sources" (p. 4, lines 19-20 [0020], variant AAT refer to functional equivalents to the native (p. 4, line 34) and "proteins that are substantially identical to a native sequence." (p. 5, line 6) Also, native AAT includes allelic and splice variants as well as truncated forms (p. 4, lines 21-22). Because of the overlap in definitions, the metes and bounds of variant vs. native AAT cannot be determined.

Claims 28-30 are duplicates of claims 5-7 and claims 31-32 are duplicates of claims 8-9.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an AAT which is a serine protease inhibitor, does not reasonably provide enablement for an AAT which does not have serine protease inhibitory activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to a pharmaceutical composition comprising an AAT, which is a native, recombinant or variant AAT, in addition to other non-protein components. Because the composition is a "pharmaceutical composition", it must have therapeutic use. Wildtype AAT is recognized as a serine proteinase (or protease) inhibitor (US 5,166,134, col. 2, lines 4-25, IDS of 1/14/08). There is no structural or functional limitation of the AAT in the claims. That is, the AAT is not claimed by specific sequence, for example, which would inherently confer a particular function or have an explicit functional requirement. It is acknowledged that there are over 100 AAT naturally occurring genetic variants known (Luisetti et al., Thorax, 59:164-9, 2004). However, the claims including an "AAT variants" include not only functional variants, but sequence variants with substitutions, deletions and/or insertions relative to a native sequence (which includes allelic and splice variants). Single amino acid changes effect the function of AAT. Van Steenbergen (Acta Clin. Belgica, 43:171, 1993) reports (paragraph beginning p. 176, col. 2) that substitution of Glu342 -> Lys342 results in a deficiency variant in which "85% of the normally synthesized polypeptide is blocked in the endoplasmic reticulum…." "Glu264 -> Val264 …does not lead to intracellular accumulation but to an early intracellular proteolysis…." of the nascent S polyp This is pharmacologically important because mutation of these residue can lead to significantly decreased plasma levels and increased risk of emphysema and liver disease (*ibid.).* Carrell et al. (Nature, 1982, IDS filed 1/14/08) showed that two AAT variants are linked to progressive loss of lung elasticity that contributes to lung damage such as emphysema (*e.g.*, p. 33, col. 2, second paragraph).

Native variants have been characterized as "normal, deficient, null and dysfunctional" (Ljujic et al., J. Biochem. Biophys. Meth. 68(3):167-173, 2006, p. 168, end of second full paragraph). Because one skilled in the art would not reasonably expect that an AAT which was not a proteinase inhibitor could be of therapeutic benefit, and because the claims encompass an AAT with no or reduced serine protease inhibitor function, the invention is not enabled for the full breadth of the claims. That is, an AAT with reduced activity compared to the normal wildtype AAT would be expected to increase a subject's risk of lung and/or liver disease and the specification has not taught how to therapeutically use such AAT molecules.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 19, 20, 22, 28-30 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,618,786 (IDS filed 1/14/08).

US 5,618,786 teaches an aerosol formulation in which recombinant AAT (col. 4, lines 16-17) is in an amount to provide 1μg to 10mg/kg of host and includes the addition of lactose (a carbohydrate; col. 3, line 10 and 16-17) from 0-80% w/v, and surfactant (*e.g.*, a diglyceride) from 10-50% w/v (col. 3, lines 10-18).

Note that because there is nothing to distinguish the structure of a native, variant and recombinant AAT in the claims, the AAT taught in US 5,618,786 appears to anticipate any/all AATs.

Claims 1-7, 10-12, and 28-30 are rejected under 35 U.S.C. 102(b) as being anticipated by US 6,267,958.

US 6,267,958 teaches a composition, which may be lyophilized that comprises AAT (col. 6, lines 49), a carbohydrate called a "lyoprotectant" such as sucrose or trehalose (col. 9, lines 21-33), a surfactant such as polysorbate 80 (col. 15, lines 36-41) and an antioxidant such as methionine (col. 16, lines 5-9). The composition is also taught reconstituted with a diluent, which includes water (*e.g.,* col. 2, lines 20-23).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 8-9, 13-27 and 31-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,267,958 as applied to claims 1-7, 10-12, and 28-30 above, and further in view of US 5,166,134 (IDS filed 1/14/08).

US 6,267,958 teaches a composition, which may be lyophilized that comprises AAT (col. 6, lines 49), a carbohydrate called a "lyoprotectant" such as sucrose or trehalose (col. 9, lines 21-33), a surfactant such as polysorbate 80 (col. 15, lines 36-41) and an antioxidant such as methionine (col. 16, lines 5-9). The composition is also taught reconstituted with a diluent, which includes water (*e.g.,* col. 2, lines 20-23). Also taught is a formulation wherein the protein concentration is at least 50 mg/ml (col. 2, lines 30-33). Further, an example of a reconstituted powder is shown wherein the protein is a HER2 antibody at a protein concentration for the prelyophilized formulation of 25 mg/ml, the carbohydrate (trehalose) concentration is 60 mM and the surfactant (Tween 20, a.k.a. polysorbate 20) concentration is 0.01% (Figs. 1 and 6). US 6,266,958 does not teach glycosylation state for AAT, carbohydrate concentrations as w/v or antioxidant concentrations.

US 5,166,134 teaches a pharmaceutical composition comprising AAT at 0.1-4.5% w/v in an aqueous solution (col. 2, lines 58-61). AAT is taught as glycosylated or unglycosylated (col. 3, lines 15-18). Also taught is the formulation comprising an antioxidant (col. 4, lines 22-23) and sorbitol solution (a surfactant, col. 4, line 26). AAT is taught (col. 2, lines 9-15) as having a "role in controlling tissue destruction by endogenous serine proteinases. A genetic deficiency of alpha-1-proteinase inhibitor [AAT], which accounts for 90% of the trypsin inhibitory capacity in blood plasma, has been shown to be associated with the development of asthma and pulmonary emphasyema." Recombinant AAT proteins and analogs prepared by site-directed mutagenesis are taught (col. 3, lines 41-47).

US 5,618,786 teaches an aerosol formulation in which recombinant AAT (col. 4, lines 16-17) is in an amount to provide 1μg to 10mg/kg of host and includes the addition of lactose (a carbohydrate; col. 3, line 10 and 16-17) from 0-80% w/v, and surfactant (*e.g.*, a diglyceride) from 10-50% w/v (col. 3, lines 10-18). AAT is taught for the treatment of, for example, emphysema and may be isolated from a natural source, prepared recombinantly or may be a mutant of the naturally occurring form (col. 2, lines 43-50). It is stated (col. 3, lines 1-4) that, "The aerosol formulation may be varied widely, depending on the nature of the therapeutic agent, whether additional agents will be included, the manner and area in which it will be released in the lungs, or the like."

It would have been obvious to the artisan of ordinary skill at the time the invention was made to have had a pharmaceutical composition comprising AAT as taught by each of the three patents cited above and further comprising a carbohydrate (*e.g.*, trehalose), surfactant (*e.g.*, polysorbate 80) and antioxidant (*e.g.*, methionine) as taught by US 6,266,958 and US 5,618,786. Such a formulation would have been desirable because of its therapeutic application for emphysema as taught by US 5,618,786. It would have been desirable for the formulation to be in a powder (solid) or liquid form. US 6,267,958 teaches lyophilized forms which are notable for their stability and ability to retain activity in a reconstituted aqueous form. It would be obvious to have had the AAT in a glycosylated or unglycosylated form produced by isolation from nature or recombinantly as taught by US 5,166,134. It reasonably appears that the ranges of carbohydrate and surfactant concentrations taught by the prior art meet the limitations of the instant claims. Additionally, for pharmaceutical compositions, optimization of concentrations within a formulation were routine.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire Kaufman, whose telephone number is (571) 272-0873. Dr. Kaufman can generally be reached Monday, Tuesday, Thursday and Friday from 9:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached at (571) 272-0835.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Official papers filed by fax should be directed to (571) 273-8300. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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